

Necrotizing Enterocolitis and Spontaneous Intestinal Perforation: A Spatiotemporal Case Cluster Analysis

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Abstract

Objective: To expand existing statistical methods to identify clusters of necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) cases in the neonatal intensive care unit. **Methods:** In an academic, tertiary referral center, possible NEC or SIP clusters were identified using a binomial distribution scan test. The incidence-density rate (IDR) was calculated as the number of cases per 1,000 patient-days during each possible cluster and compared with the baseline IDR. A structured chart review compared cluster and noncluster cases. Spatial clustering analyzed the physical distribution of cases using the Grimson Test. Repeat analysis included only SIP cases. **Result:** The initial scan identified 3 suspected temporal clusters. IDR comparison confirmed only 1 cluster. Analysis of SIP only cases revealed similar results. Physical proximity was not a significant factor. Chart review of the SIP and NEC cases revealed significant increases during the confirmed cluster of small for gestational age infant births and indomethacin treatment. Chart review of the SIP only cases in the confirmed cluster revealed no significant differences. **Conclusion:** Statistical methods distinguish whether suspected case clusters represent a significant increase in baseline incidence. True clusters warrant detailed investigation including spatial analysis and chart review. This approach may have application in other disease processes and populations. (*Pediatr Qual Saf* 2019;4:e127; doi: 10.1097/pq9.000000000000127; Published online January 4, 2019.)

INTRODUCTION

The clinically distinct entities of spontaneous intestinal perforation (SIP) and necrotizing enterocolitis (NEC) are important causes of mortality and morbidity in premature and low-birth-weight infants.¹⁻⁵ Although distinct, these 2 diseases have considerable overlap in their presenting symptoms and management. Furthermore, a definitive diagnosis is made operatively though not all patients undergo exploratory laparotomy during the acute phase of illness.⁶ The combined incidence of SIP and severe NEC (defined as the presence

of free air or clinical deterioration requiring operative intervention) is estimated from 5% to 9% in extremely low-birth-weight infants at Neonatal Research Network Centers.^{6,7} Though SIP and NEC typically occur sporadically, NEC outbreaks do occur.⁸ The etiology is usually infectious, generally of viral origin.⁹⁻¹¹ The etiology of SIP is unknown, but is associated with chorioamnionitis, indomethacin, and glucocorticoid administration.¹²⁻¹⁵

Disease outbreaks represent potential safety events amenable to cluster investigations.¹⁶ Such investigations led to historically significant epidemiological breakthroughs in the study of infectious diseases.^{17,18} In the hospital setting, cluster investigations can be particularly useful as inpatient records may more accurately pinpoint disease onset and uncover exposures. Although staff reports commonly initiate cluster investigations, statistical methods have been developed to identify disease time and space clusters.¹⁶ Previous outbreaks of NEC were analyzed with statistical methods.^{17,19,20}

Early identification of disease outbreaks in the hospital is aligned with the quality and safety movement. The provision of safe, high-quality, medical care is inwardly guided by the profession's underlying commitment to nonmaleficence and outwardly directed by public demand, legislative requirements, and market forces.²¹⁻²⁴ The quality and safety movement aims to ensure optimal patient outcomes at a permissible financial cost.^{25,26} Hospitals often strive to monitor and affect the quality and safety of care



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provided in real-time by adapting best practices from manufacturing.^{27,28} As estimates of preventable harm rise, novel strategies for monitoring and identifying potential safety events are increasingly necessary.^{29–31}

Eight patients in our NICU developed SIP or NEC within 29 days in the spring of 2013. Our objective was to apply and expand existing statistical methods to identify clusters of severe NEC and SIP cases in the NICU with a secondary goal of creating a generalizable set of statistical methods to analyze potential disease outbreaks.

METHODS

The institutional review board approved this retrospective review of records.

Patients

Patients included in this study were born at Women and Infants Hospital and experienced spontaneous intestinal perforation or severe necrotizing enterocolitis requiring operative intervention. We excluded nonoperative NEC cases. Operative interventions included both laparotomy and peritoneal drain placement. NEC or SIP was definitively diagnosed at laparotomy. If the infant underwent peritoneal drain placement only, then a clinical diagnosis of SIP was made by lack of pneumatosis, patient characteristics (age, feeding status, and acuity of onset and severity of illness), and pattern of resolution of the illness.

Setting

Women and Infants is an academic, freestanding, specialty hospital with more than 8,000 deliveries per year. The 80-bed, single-family room, level IV NICU is a regional referral center that admits over 1,200 infants annually. Eight “neighborhoods” house single-family rooms and share nursing and ancillary staff. A single general pediatric surgical group based at the adjacent children’s hospital provides surgical support for the unit. A patient list from the pediatric surgery group’s consultation log contained patient information and indication for all surgical NICU consultations from March 1, 2011 to June 30, 2013. This list served as the basis of our cohorts.

Analytical Approach—Step 1: Scan Test to Identify Suspected Case Clusters

Using an approach previously described by Meinzen-Derr to analyze a series of NEC cases in their NICU, we first performed a scan test to identify possible case clusters.¹⁹ The scan test, originally described by Grimson and Mendelsohn as a way to monitor calls at poison centers, uses the binomial distribution to detect current clusters during ongoing data collection.³² This test compares the number of events in a time-window to the number of events in a larger time-frame to determine if the number of events in the time-window is significantly larger and, hence, comprise a potential cluster.

We applied the scan test using a 30-day window to scan the time frame of 28 months, for which surgical data were available. The reason for a 30-day window was to increase the chance of identification of clusters not readily apparent to simple observation. The *P* value was calculated based on the cumulative cases of SIP and NEC cases in each window. A *P* value of <0.05 was considered statistically significant.

Analytical Approach—Step 2: Incidence Density Rate to Confirm Case Clusters

Again following the model proposed by Meinzen-Derr, we next calculated the incidence-density rate (IDR), defined as the number of newly developed SIP and severe NEC cases per 1,000 patient-days, for the time-window of interest. The purpose of the IDR comparison was to determine whether the suspected cluster rates of SIP and severe NEC cases were significantly higher than the expected rate, controlling for the patient census. We compared suspected cluster IDR to the baseline IDR for the period for which data were available. A Fisher’s exact *P* value <0.01 was used to determine statistical significance, which duplicates the Meinzen-Derr model. This analysis applies stricter criteria to the IDR test to set a higher threshold for significance on a repeated test. The exact adjustments behind determining the *P* value are not detailed by Meinzen-Derr, but our goal was to duplicate the model.

The IDR above uses total patient days as a denominator. However, SIP and NEC are markedly more common in very low–birth-weight infants (VLBW, <1500 g), and as such, the IDR may not represent the true number of at-risk patients. Thus, we obtained the monthly number of VLBW infants admitted from departmental admission logs and calculated the median and SD. The monthly VLBW admissions during the confirmed clusters compared with the median, using the z-score, determined if there was a significant increase in VLBW admissions during that cluster.

Analytical Approach—Step 3: Spatial Analysis of Confirmed Case Clusters

To identify any contribution from the proximity of patient rooms and concomitant contact with medical personnel (eg, nurses), retrospective spatial clustering analysis compared cases identified in step 2 using the Grimson Test for spatial clustering.^{18,33} This test compared the distribution of the SIP and severe NEC cases with the assumption that there is a random distribution of ill persons throughout the NICU. Medical records showed the bed assignments of confirmed case clusters. A patient room was considered physically related to all other rooms in a given neighborhood (Fig. 3). A *P* value of <0.05 was used to determine statistical significance.

We repeated the analysis a second time including only SIP cases to determine if case clusters of SIP existed independently from severe NEC.

Table 1. Structured Chart Review

Antenatal factors
Maternal age
Maternal gravid and parity
Multiple gestation
Maternal medical history
Duration of rupture of membranes to delivery
Antenatal steroids
Infant characteristics
Gestational age
Birth weight
Reason and mode of delivery
Ventilation history
Surfactant administration
Postnatal steroid administration
Presence of patent ductus arteriosus with administration of indomethacin or surgery
Prophylactic indomethacin administration
Feeding history
Administration of antibiotics and culture results
Blood transfusion

Analytical Approach—Step 4: Structures Chart Review of Confirmed Case Clusters

A structured, retrospective chart review proceeded case clusters established by the methods described above with the goal to identify statistical differences between infants in a case cluster and those in the noncluster group. Although the most significant risk factors described in the literature for SIP and NEC are prematurity and low birth weight, additional risk factors include enteral feeding, bacterial infection, antenatal factors, and indomethacin use.^{34–36} Table 1 lists the data reviewed from the medical record. Continuous variables (gestational age, birth weight, maternal age) were compared using the Wilcoxon rank sum test, and the remaining categorical variables were treated as proportions and compared using the Fisher’s exact test. A *P* value of <0.05 was used to determine statistical significance.

Excel 2007 and Python 2.7 with additional packages: Numpy 1.8.0, Scipy 0.13.0 processed statistical analyses. Statistics Online Computational Resource³⁷ calculated the Wilcoxon rank sum comparison.

Findings were disseminated to staff at the department’s multidisciplinary, monthly Mortality and Morbidity conference.

RESULTS

Over 28 months, there were 21 total operative cases of SIP or severe NEC resulting in an overall IDR of 0.4 cases/1,000 patient days. The initial scan identified 3 suspected clusters in the spring of 2012 (3 cases), fall of 2012 (3 cases), and the spring of 2013 (7 cases; Fig. 1A). Analysis of only SIP cases revealed 16 of the 21 cases were due to SIP, with an SIP IDR of 0.3. Again, 3 suspected clusters were identified in the initial scan in the spring of 2012 (2 cases), fall of 2012 (2 cases), and spring of 2013 (5 cases; Fig. 1B).

After comparing the baseline IDR with the IDR in the suspected clusters, only the suspected cluster in 2013 was found to represent a confirmed cluster (*P* < 0.01) of SIP and severe NEC cases (Fig. 2A). Suspected clusters 1 and 2 had nonsignificant *P* values: 0.03 and 0.04, respectively, above the designated *P* value of 0.01 used in Step 2. The SIP only analysis again found only the confirmed cluster (*P* < 0.01) in the spring of 2013 (Fig. 2B). Suspected clusters 1 and 2 in the SIP only analysis had nonsignificant *P* values: 0.09 and 0.1, respectively.

Room location with concomitant contact with medical personnel was not found to contribute to the combined cases (*P* = 0.75; Fig. 3A) and SIP only cases (*P* = 0.72; Fig. 3B).

Statistically, hospital staff admitted no more VLBW infants during the cluster months than during other months in the relevant period. Specifically, during the confirmed cluster in the spring of 2013, admissions of VLBW patients in the relevant months of April and May were 21 and 22, respectively. Compared with the average of 17 admissions per month, the admission increase was not significant (*P* = 0.17 and *P* = 0.11, respectively).

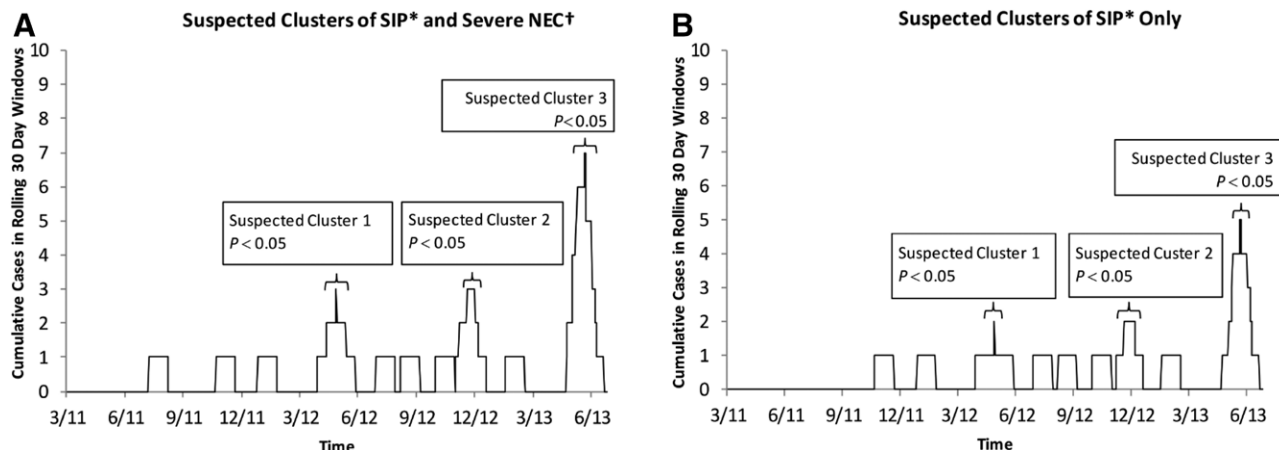


Fig. 1. Cumulative disease cases in rolling 30-day windows for SIP and Severe NEC or SIP Only. *Spontaneous intestinal perforation, †necrotizing enterocolitis requiring surgical intervention.

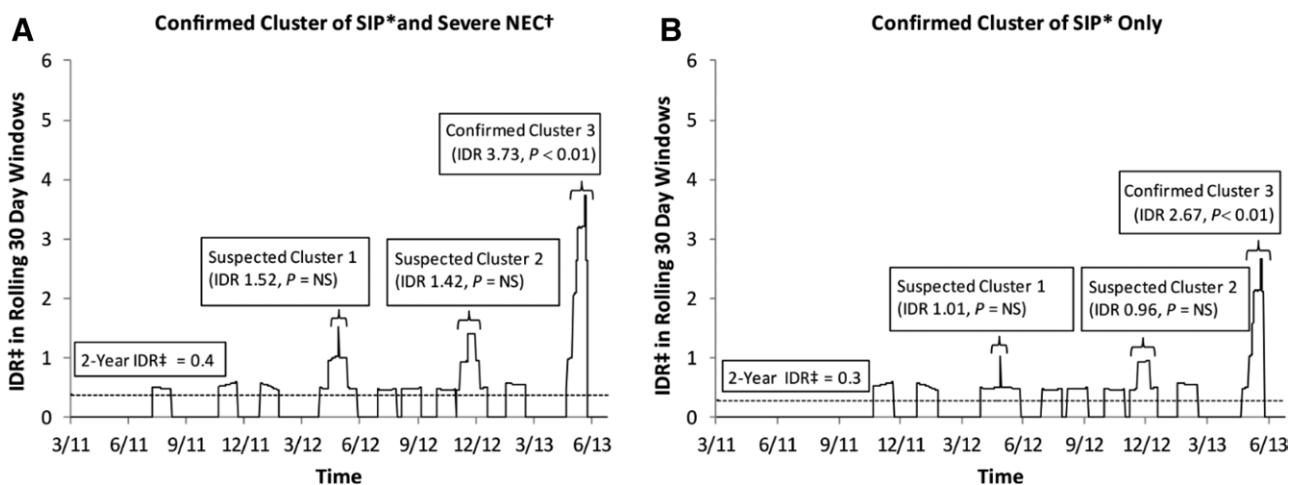


Fig. 2. Cumulative disease cases in rolling 30-day windows for SIP and Severe NEC or SIP Only plotted against 2-year IDR. *Spontaneous intestinal perforation, †necrotizing enterocolitis requiring surgical intervention, ‡incidence density ratio.

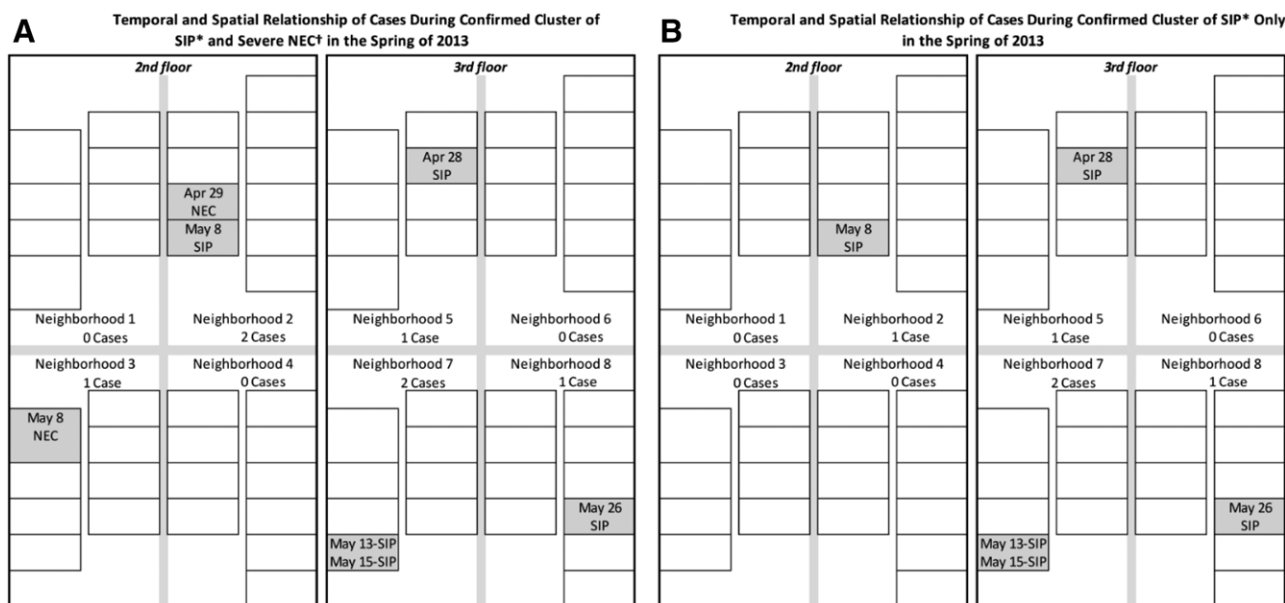


Fig. 3. Location of SIP and Severe NEC cases during the confirmed cluster in spring 2013. *Spontaneous intestinal perforation, †necrotizing enterocolitis requiring surgical intervention.

Chart review of the SIP and severe NEC cases in the confirmed cluster compared with noncluster SIP and severe NEC yielded no significant differences in maternal characteristics (Table 2). A comparison of infant characteristics identified statistically significant differences in small for gestational age status at birth and indomethacin treatment for patent ductus arteriosus (Table 3). Note, 1 patient received indomethacin for a suspected patent ductus arteriosus (PDA) before receiving an echocardiogram. SIP cases in the confirmed cluster compared with noncluster SIP cases showed no unique prenatal, intrapartum, or postnatal risk factors (Tables 2, 3). Of note, while the cases in the confirmed clusters did not have a significantly increased number of positive cultures, 3 SIP cluster cases were positive for

coagulase-negative *Staphylococcus*, *Staphylococcus epidermidis*, and *Staphylococcus capitis*, respectively. SIP noncluster cases showed similar culture data.

DISCUSSION

In summary, we present a temporal cluster of SIP and severe NEC cases. Statistical methods evaluating the incidence and rate of disease showed a significant increase in SIP and severe NEC in the spring of 2013. Admission records reveal that there was no significant increase in vulnerable VLBW patients in the unit during this period. Chart review did not reveal any single etiology.

Among the clustered SIP and severe NEC cases, there were more small for gestational age infants at birth and

Table 2. Maternal Characteristics

Maternal Characteristic	Clustered SIP and NEC (n = 7)	Non-clustered SIP and NEC (n = 14)	P	Clustered SIP Only (n = 5)	Non-clustered SIP Only (n = 11)	P
Mean age (y) (range)	26 (18–35)	25.6 (16–40)	0.90	23.4 (18–33)	25.4 (16–33)	0.57
Mean number of the pregnancy (range)	1.6 (1–2)	2.6 (1–7)	0.13	1.6 (1–2)	2.5 (1–7)	0.28
Mean parity (range)	1.7 (1–3)	1.6 (1–3)	0.71	2.0 (1–3)	1.6 (1–3)	0.45
Cesarean section, n (%)	3 (42)	7 (50)	0.45	3 (60)	6 (55)	1.00
Prenatal care, n (%)	7 (100)	14 (100)	1.00	5 (100)	11 (100)	1.00
Maternal chorioamnionitis, n (%)	2 (29)	2 (14)	0.28	1 (20)	2 (18)	1.00
Hypertension, n (%)	1 (14)	2 (14)	1.00	1 (20)	1 (9)	0.46
Antibiotic therapy, n (%)	3 (43)	6 (43)	1.00	2 (40)	4 (36)	1.00
ROM > 18 h, n (%)	0	2 (14)	0.28	0	1 (9)	0.69
Antenatal indomethacin, n (%)	1 (14)	4 (29)	0.40	0	4 (36)	0.18
Antenatal steroids, n (%)	7 (100)	11 (79)	0.28	5 (100)	9 (82)	0.26

ROM, rupture of membranes.

Table 3. Infant Characteristics

Infant Characteristic	Clustered SIP and NEC (n = 7)	Non-clustered SIP and NEC (n = 14)	P	Clustered SIP Only (n = 5)	Non-clustered SIP Only (n = 11)	P
Male, n (%)	4 (57)	6 (43)	0.44	4 (80)	6 (55)	0.36
Mean gestational age (wk) (range)	25.6 (23–28)	27.0 (23–33)	0.29	26.1 (24–28)	26.4 (24–33)	0.86
Multiple births, n (%)	3 (43)	2 (14)	0.03	2 (40)	2 (18)	0.26
Mean birth weight, g (range)	751.4 (520–970)	992.7 (560–2,190)	0.19	786 (520–970)	899.8 (560–1,760)	0.50
Small for gestational age, n (%)	3 (43)	0	0.03	2 (40)	0	0.08
Inborn, n (%)	7 (100)	12 (86)	0.28	5 (100)	9 (81)	0.26
Intubation after birth, n (%)	7 (100)	10 (71)	0.09	5 (100)	9 (81)	0.26
Surfactant administration*	6 (86)	10 (71)	0.40	4 (80)	9 (81)	1.00
PDA on echo*, n (%)	3 (43)	1 (7)	0.08	2 (40)	1 (9)	0.20
Indomethacin for PDA, n (%)	3 (43)	0	0.02	1 (20)	0	0.31
Surgery for PDA	0	0		0	0	
Mean days of enteral feeds* (range)	10.3 (0–31)	6.0 (0–30)	0.37	3.0 (0–7)	2.3 (0–6)	0.62
Transfusion 24 hours*, n (%)	1 (14)	3 (21)	0.40	0	3 (27.2)	0.26
Postnatal steroids*	0	0		0	0	
Mean days of antibiotics* (range)	8.7 (2–23)	4.8 (3–12)	0.07	5.4 (2–9)	3 (3–7)	0.22
Prophylactic indomethacin, n (%)	7 (100)	11 (79)	0.28	5 (100)	10 (91)	0.69

*Before event.

PDA treatment with indomethacin than in the nonclustered cases. Both small for gestational age and PDA treatment are known risk factors for NEC, implying that the patient population may have been at a higher risk than previously thought.

When the SIP cases were analyzed separately from the severe NEC cases, there was still a significant increase in cases in the spring of 2013, but chart review did not reveal any significant differences between the cluster and noncluster cases. This finding may be due to the smaller number of patients in the SIP only group.

We used a standard, generalizable approach that could be used to identify other disease outbreaks in the NICU. Although case cluster analysis has been historically used for identifying infectious outbreaks, this approach may also highlight unintended consequences of changes in clinical practice. The methods we propose can be used to detect clusters in real-time, allowing the medical team to investigate and alter the NICU environment as needed. For example, in the future, the scan test could be integrated into the electronic medical record and set to run daily. Any positive findings would then warrant further investigation for a common exposure through spatial analysis and chart review. Furthermore, the methods used in this study can be applied to rare events and show the value of using a statistical perspective when a few cases

above the baseline may be overlooked when using only heuristics.

The scan test is quick to implement and only requires a list of dates of occurrence for the event of interest. As it does not account for the changing population in the NICU, so the IDR comparison is needed to identify increases in the rate of disease. The IDR comparison requires more data to implement, requiring a measure of the denominator of interest. If the electronic medical record allows for easy querying of this patient count, the IDR comparison is straight-forward.

Spatial analysis of a case cluster would ideally include a thorough mapping of all providers who had contact with the identified cases, paying special attention to those providers who reported symptoms around the time of the cluster. Although the Grimson Test is a good initial step in evaluating the geographic distribution of the cases, it does not account for the variability of provider location throughout the cluster period. We need further study to develop a detailed yet simple approach to provider-influenced outbreaks.

Although the statistical methods described in this article are not specific to neonatal pathology, one possible application of these methods is to apply them to medical NEC. As discussed earlier, medical NEC has been associated with outbreaks of viral origin and applying these

methods to all cases of NEC could potentially result in interventions to improve outcomes in the NICU. An automated report of the scan test could be scheduled to run daily with results given to the medical staff for review. As stated above, positive findings would prompt further analyses.

As SIP and NEC are thought to represent distinct diseases, and as there are no published reports of SIP outbreaks, it was necessary to analyze SIP cases independently. As noted, a temporal cluster of SIP cases occurred in the spring of 2013, but chart review did not reveal a common etiology. The lack of significance in the chart review may be due to the small number of cases (only 5 SIP cases in the cluster). Further study is needed to investigate possible causes of this SIP temporal cluster.

A temporal cluster suggests an infectious cause or, at least, a common exposure. In this retrospective analysis, many of the patients received no microbiology testing such as fluid cultures or viral studies, so it is difficult to compare the infectious aspects of the cluster and noncluster cases. Infectious etiologies for NEC outbreaks were identified in the literature, but SIP is not viewed as an infectious process. Still, positive peritoneal and blood cultures in SIP patients have caused some to speculate on an infectious origin. Bacterial and viral studies would be useful in future investigations.

Due to the difficulty of diagnosis, we included severe NEC and SIP cases together.²⁵ The primary diagnostic tool in our study was radiologic imaging. In the future, novel biomarkers may be used to differentiate NEC from SIP further.

In summary, novel statistical methods may help distinguish whether case clusters represent a true temporal increase above baseline incidence. Identification of temporal clusters direct systematic case review and analysis of contributing practice variations. This approach may add value to other disease processes and populations within and between hospitals.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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